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# T lymphocytes and aortic aneurysms

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Aortic aneurysms are common and life threatening problems with high rates of death. The initiation and progression of aneurysms are characterized by extensive extracellular matrix degradation and immune cells invasion within arterial wall. During the pathogenesis of all aneurysms, inflammation and immune cells play a significant role. Although T cells are abundant in aneurysm tissue, their functions in initiation and propagation of aneurysms remain unclear. This review summarizes the current state of knowledge of T lymphocytes on this disease and focuses on potential mechanisms of specific T cell responses.

**T cells, cytokines, aortic aneurysms, inflammation, pathogenesis**

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Aortic aneurysms, the common life-threatening problem, have been recognized as major causes of death for centuries [1,2]. Because of the silence without symptoms and predisposition for rupture, aortic aneurysms always go undetected until fatal rupture which contributes to 80%–90% mortality [1,3]. Aneurysms can develop in any artery and therefore be classified by anatomic location, such as coronary artery aneurysms [4,5], intracranial artery aneurysms (IAs) [6–8]. There are two predominant distributions of aortic aneurysms in patients. One is abdominal aortic aneurysm (AAA), the most common form that is typically associated with but independent of atherosclerosis [9]. The second common type is thoracic aortic aneurysms (TAA) which is highly associated with hereditary influences and show less association with atherosclerosis [1,10,11]. All of these aneurysms share many similar features in common, while having different physical structures which contribute to the different pathologies in origin and evolution [11].

Recently, accumulated reports suggest that aneurysms may not arise entirely through atherosclerosis and, at least, many other etiologic factors are also involved in the disease development. Atherosclerosis may not directly cause AAA, but can trigger the first inflammation to induce the infiltrates. The underlying causes could be atherosclerosis, tobacco smoking, familial clustering, genetic background and environmental factors [9,12].

The main organization of aortic wall includes elastin and collagen: elastic fibres and smooth muscle cells in the media are required for mechanical properties of the aorta; collagen (especially types I and III) in adventitia maintains structural integrity. Elastin fragmentation and medial attenuation are the most histological features of aneurysm development, while adventitial collagen degradation ultimately favors the rupture. Besides, VSMCs apoptosis also has an effect on vessel wall weakening [11]. The alterations and remodeling of these connective tissues resulted from proteases production. Medial smooth muscle cells (SMCs), adventitial fibroblasts and inflammatory cells are the main sources of these matrix-degrading proteases [2,9,13]. The infiltration cells in all layers of the wall, most important pathologic features of aneurysms, include monocytes, lym-

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phocytes and plasma cells. In addition to release proteases, these cells secrete overwhelming inflammatory cytokines and participate in the destruction of the aortic wall and progression of enlargement and rupture [9,14,15]. Lymphocytes, apart from macrophages, are the predominant inflammatory cells found in aneurysm tissue [15,16]. Therefore, understanding the pathogenesis of T cells in aneurysms has become increasingly prior and will provide important insights into basic research and clinical practice. So far, some potential pathogenic mechanisms of formation and development of this disease have been found. Here we focus on the current mechanisms of T cells in the development of aortic aneurysms.

## 1 T cells in aneurysms

Not only elastin fragments, but also the production of proinflammatory cytokines, chemokines by immune cells themselves promote the T cells recruitment into the wall [9]. Immunohistochemical staining and flow cytometry suggested that elevated numbers of $CD3^+$ cells (include both $CD3^+$ $TCR\alpha\beta^+$ and $CD3^+$ $TCR\gamma\delta^+$ cells), localizing in aortic media and adventitia, were present in aneurysm patients [16,17], which may further led to the death of VSMCs [18]. With the evidence that oligoclonal αβ TCR+T cell populations expansion in aneurysmal lesions from AAA patients, AAA is considered as a specific antigen-driven T cell disease [19,20]. The T cell co-stimulatory factors CD28 and CTLA-4, as well as their ligands CD80 and CD86 have been found in AAA patients, with sCD28 and sCD86 increased and sCTLA-4 decreased in plasma. Although they failed to predict the size of aneurysm, sCTLA-4 and sCD80 levels were correlated negatively with matrix metalloprotienase-9 (MMP-9) [21].

Although T-cell immunodeficiency has been reported to develop progressive intracranial aneurysms in 15-year-old patients [22], lymphocyte deficiency may not affect AAA formation in *Rag-1*$^{-/-}$ mice [23]. The fact that *Rag-1* deficiency influences not only T cells but also non-lymphocytic leukocyte populations may be responsible for it. Furthermore, it should be noted that different T cell subsets have complex effects during inflammatory response and may even counteract each other.

## 2 $CD4^+$ T cell subsets in artery aneurysms

The inflammatory infiltrate in the aortic wall in aneurysms is dominated by $CD4^+$ T cells with activated memory phenotype. Naïve $CD4^+$T cells have been divided into several subsets by the ability to produce specific cytokines. Th1 and Th2 subsets are characterized by production of IFN-γ and IL-4 respectively, which may drive opposing effects on immune process. Natural regulatory T ($nT_{reg}$) cells and induced $T_{reg}$ ($iT_{reg}$) cells can produce TGF-β, IL-10 and IL-35. Th17 cells produce IL-17A and IL-17F as their signature cytokines. Studies described below show evidence of these subsets in aneurysms of both mice and human. We also highlight the possible mechanisms.

## 3 Th1 cells

Several reports consider Th1 as predominant type of $CD4^+$T in AAA [17,24–30]. Galle [26] and Tang et al. [31] identified $CD4^+$ T cells production of high levels of IFN-γ but not IL-4 in human aneurysmal aortic lesion from both gene and protein levels. Overexpression of the transcription factor T-bet and the absence of GATA-3 expression further proved the Th1 cells participating in human AAA lesions. Furthermore, in terms of function, Xiong et al. [24] confirmed the contributions of Th1 cells and IFN-γ in the development of AAA. AAA formation was suppressed in CD4-deficient (*CD4*$^{-/-}$) mice or IFN-γ-deficient (*IFN-γ*$^{-/-}$) mice, whereas IFN-γ could partially reconstitute aneurysms with restored levels of matrix metalloproteinase-2 (MMP-2) and -9 (MMP-9) secreting by SMCs and macrophages, respectively [24]. Chan et al. [25] suggested that IFN-γ could increase Fas expression in VSMCs, thereby inducing VSMC apoptosis. In addition, the observations that IFN-γ can cause type I and III collagen reduction [32,33] may also account for its role in progression of aneurysms. In particular, Th1 cells positively correlate with increased aortic external diameter and expansion in aneurysm patients [31]. In line with these findings, the elevated levels of IFN-γ may predict aneurysm expansion in patients [28].

Although confirming IFN-γ-producing Th1 cells as the master regulators, results from some research, by contrast, suggest the protection role of Th1 cells in aneurysms. Shimizu et al. [34] found that IFN-γ receptor-deficient (GRKO) mice had an increased incidence of aneurysm formation and spontaneous rupture, thereby implying the protective role of IFN-γ in aneurysms. Similar to these findings, King et al. [35] confirmed the protective role of IFN-γ in aneurysms. They suggested that IFN-γ deficiency (*IFN-γ*$^{-/-}$) led to increased incidence of AAAs in Ang II treated apolipoprotein E deficient (*ApoE*$^{-/-}$) mice. The deletion of CXCL 10, an IFN-γ-inducible effector T-cell chemokine, resulted in high rates of death to aortic rupture in Ang II-infused AAA mice. Taken together, IFN-γ may protect against elastin degradation and inhibit aneurysm formation [34].

However, other cell types such as NK cells, NKT cells, macrophages and SMCs can also release high amounts of IFN-γ, which may have complex impact on the aneurysm formation [25,26]. Thus, the results may be multiplied by the following factors. Firstly, the difference in the temporal accumulation of different cell types could interfere with the

evaluation of IFN-γ production by Th1 cells, which may shake the Th1 predominance. Besides, the signaling pathway by direct cell contact may be different from indirect action of cytokines. For instance, the protection role of Th1 cells interaction with the resident vascular wall cells may be counterbalanced by IFN-γ, the proinflammatory cytokine that promotes the death of VSMCs. Most importantly, IFN-γ may enhance the proliferation and function of other immune cells which exert opposite effects on AAA pathogenesis, therefore, counteracting the effects of IFN-γ.

## 4 Th2 cells

Other groups have found evidence that the AAA infiltrates are predominantly IL-4-produicng Type 2 lymphoid cells [21,34,36–40], which contrasts with previous studies suggesting the predominance of Th1 disorder. Schonbeck et al. [36], the first group supporting the dominant expression of Th2 response in AAA, found that there were difference between AAA and stenosis atheroma in the $CD4^+$ T cell predominance. AAA tissues showed elevated levels of Th2 associated cytokines IL-4, IL-5 and IL-10, but little or no expression of Th1 producing cytokines. In contrast, extracts of human atherosclerotic plaques expressed high levels of characteristic Th1 cytokines rather than Th2 cytokines. Not only having been proved in mice model, Th2-predominant inflammation has also been found in patients with coronary artery ectasia (CAE). The decreased levels of serum TNF-α and IL-18, strong Th1 stimulating cytokines, indicated the lack of Th1 cells response and the predominance of Th2 in CAE patients [38].

By expressing high levels of Fas-associated phosphatase (FAP-1), Th2 subset inhibits Fas signaling and causes death of Th1 cells, and even SMCs in AAA. Additionally, IL-4 induces the expression of MMP-1 and MMP3 in mononuclear phagocytes and SMCs, which enhances the collagenolytic and elastolytic activities. All of these demonstrate a Th2 immune pattern of matrix-degrading enzymes in AAA different from Th1 predominant immune response in atherosclerosis [36]. Shimuzu et al. [34] extended this theory in an allografted aortas model. Aortic allografts in IFN-γ receptor-deficient (GRKO) recipients resulted in the development of aortic aneurysms, which suggested IL-4 predominance response. This IL-4-driven inflammation model showed high levels of MM-9 and MMP-12. On the other hand, GRKO recipients with IL-4 blockade resulted in prevention of aortic aneurysm formation and showed minimum of elastic degradation. They further found that IL-4 improved and IFN-γ diminished MMP-9 and -12 expression in macrophages, suggesting a new finding that Th2 and IL-4 can act as important stimulus to AAA formation.

Although IL-4 attracts more particular interest among prototypical Th2 cytokines, recent research shows that the elevation of IL-5, another Th2 cytokine, is present in the early phase of Ang-II induced AAA formation. The inhibition of IL-5 could prevent AAA development, which is associated with the failure in up-regulation of MMP-2 and MMP-9. Potential mechanisms that are involved include the regulation of IL-5 in both innate and acquired immunity, and the direct roles of IL-5 on SMCs [39].

Some reports demonstrated that IL-13, in pulmonary diseases, acted as potent stimulator of MMPs (especially MMP-2, -9, -12, -13 and -14) and cathepsins (such as cathepsin B, S, L, H, and K) [41,42]. However, the lack of evidence that IL-13 leads to MMPs up-regulation in aneurysms forces us to identify its contribution to aneurysm formation and development.

However, two points are worth highlighting here about Th2 cells in aneurysms. Firstly, since Th2 cytokines are usually considered as strong anti-inflammatory mediators, why can they drive proinflammatory activities in aneurysms? Secondly, why are there apparent contradictions on the predominance of $CD4^+$ T cell subsets?

Th2 cytokines can lead to a proinflammatory response in some models such as allergic asthma. Therefore, there is reason to believe that traditional anti-inflammation cytokines may have proinflammatory effects in aneurysms: IL-4 increases elastolytic activities; IL-5 up-regulates MMP-2 and -9 levels; IL-13 induces MMP-2, -9, -12, -13, and -14 expression.

Which type of $CD4^+$ T cells predominantly mediates in aneurysm degeneration has not been concluded yet, and these discordant findings may result from several aspects. Since AAA formation does not necessarily require preexisting atherosclerosis and there are considerable differences between them [43], the mechanisms initiating and stimulating progression of aneurysms remain poorly understood. Therefore, it is possible that the shared environmental (such as smoking, hypertension and obesity) and genetic risk factors (such as family history, a locus on chromosome 9p21 or 19q13) may interfuse and perplex the mechanism of aneurysms [44]. In addition, there are several types of aneurysms and the pathogenesis of them is different [3]. The stage and size of aneurysm may also contribute to the degree of elastin and collagen degradation [12], followed by different $CD4^+$ T cells infiltration including a Th1/Th2 balance or a shift to Th1/Th2.

It is not odd that Th1 or Th2 participates in the early phase of some types of aneurysm and the other appears in the later phase. But we wonder what exactly these cells are during the distinct phases and how these cells response in the aneurysm formation. The most likely mechanisms that integrate the current data regarding Th1 and Th2 response are as follows. In atherosclerosis based aneurysms, Th1 cells potentiate atherosclerosis and macrophages are also needed for the initial inflammatory cell recruitment. However, this Th1-dominated obstructive pathway is not enough to develop aneurysms, which require further stimulus. The potential secondary triggers that initiate the aneurysm stage

are the risk factors of aging and smoking. Both of the factors induce large amounts of IL-4 yet suppress IFN-γ production, which elicits Th2 dominance milieu and inhibit the Th1 cytokine signaling. Moreover, by secreting cytokines, Th2 cells could further restrict Th1 cells reaction but favor themselves. Thus, the Th1 predominant response shifts to Th2 predominance and aneurysms will develop. Therefore, the depletion of IFN-γ or other Th1 cytokines leads to the reduction of initial inflammation, followed by diminished proteases activity and protection of aneurysms. Targeting cigarettes and ages and blocking Th2 related cytokines will prevent aneurysms from dilation and rupture [12,15,45].

Of note, all the theories should take into account that NK and NKT cells can also produce Th1 and Th2 cytokines (IFN-γ and IL-4). In order to elucidate the nature and unique role of T lymphocytes, future research should use both T and NK markers to characterize cell subsets infiltration in aneurysms [37].

## 5 Th17 cells

There is a significant increase of IL-17 and IL-23 expression in human aortic tissue of AAA patients. Besides, $CD4^+$ T cells from aortic walls of WT mice showed high production of IL-17. The contribution of IL-17 in aneurysm development may be related to its role in modulating SMCs activation. Therefore, the depletion of IL-17 showed attenuated aortic diameter and cytokine production [46]. This theory was confirmed by Ju et al. [47], who found that IL-6-signal transducer and activator of transcription-3 (IL-6-STAT3) signaling pathway contributed to Th17 recruitment, promoting aneurysm formation.

On the contrary, the protection role of IL-17 is documented by other groups [48–50]. Depletion of STAT3 in T cells, as a result of overexpression of suppressor of cytokine signaling 3 (SOCS3-Tg mice), led to decreased IL-17 production. Thus, repopulation of C57BL/6 mice with SOCS3-Tg bone marrow, or adoptive transfer of SOCS3-Tg $CD4^+$ T cells in $Rag^{-/-}$ mice markedly increased the severity and mortality of AAA, with elevated accumulation of macrophages in the wall. The deficiency of STAT3 signaling in T cells, rather than in macrophages or in neutrophils, contributed to AAA formation [48]. *In vivo* suppression of STAT3 signaling or blockade of IL-17A aggravated AAA in mice as shown by increased aneurysm incidence, as well as severity and mortality from fatal rupture [49]. Furthermore, Xiong et al. [50] found that expression of IL-23 and IL-17 decreased in mice aneurysm tissues. The absence of IL-23 resulted in enlarged aneurysms with high levels of MMP-2 and -9, which suggested a protective role for IL-23-IL-17 axis in AAA development. All these findings indicate that Th17 cells play a protective role in the development of AAA.

Madhur's research [51], however, suggested that IL-17A did not influence aneurysm development. Despite that IL-17A promotes the aortic inflammatory cell recruitment, this cytokine showed no effect on aneurysm formation and extracellular matrix degradation.

## 6 Regulatory T cells (Tregs)

$CD4^+CD25^+$ regulatory T cells (Tregs), with the key expression of transcription factor Foxp3, are a subpopulation of $CD4^+$ T cells dispensable for immune self-tolerance and homeostasis. The majority of natural Treg cells (nTregs) derive from thymus, while others differentiate from peripheral naïve conventional T cells (Tconv), known as induced Treg cells (iTegs) [52]. One mode of action of Tregs in suppression of various effector lymphocytes is by inhibitory cytokines, mainly including IL-10, TGF-β and IL-35 [53]. It seemed that Tregs and its cytokines play a protective role in aneurysms. However, it is not always the case.

It is documented that reduced number and function of $CD4^+CD25^+FOXP3^+$ Tregs in aneurysm patients contribute to aneurysm pathogenesis and may predict resistance to therapy in some cases [54–56]. Inhibition of Tregs in CD25-specific antibody blockade or $CD80^{-/-}/CD86^{-/-}$ mice model showed promotion of AAA development and rupture. Furthermore, marked limitation of aneurysm development was seen in $CD28^{-/-}$ mice with Tregs supplement. The deficiency of Treg cells was associated with a blunted IL-10 and $IL\text{-}10^{-/-}$ mice showed increased susceptibility to AAA, suggesting an IL-10 dependent way for the protective role of Tregs [57]. Exogenous IL-10 into AAA explants from patients could reduce the production of IL-6, and more importantly, played a protective role in modulating AAA immune networks [58].

The activity of TGF-β, another cytokine of Tregs, was identified to prevent aneurysm progression [59–61]. Systemic inhibition of TGF-β failed to protect mice from AAA formation and rupture, associated with increased accumulation of macrophages and T lymphocytes, great loss of SMCs and enhanced degradation of elastin. The up-regulation of MMP-12 activity in anti-TGF-β treated mice also contributed to aneurysm formation [59]. Overexpression of TGF-β in hearts of $ApoE^{-/-}$ transgene mice showed less T cell infiltration, more collagen, reduced inflammatory cytokines and MMP-13, as well as increased metalloproteinase-2, with suppression of aneurysm formation [60]. However, TGF-β may have multi-functional effect on aneurysms. Kawasaki disease (KD) is characterized by inflammation, as well as coronary aneurysms. Coronary artery tissues from KD patients were used to determine the role of TGF-β in aneurysms. Despite that TGF-β facilitates the differentiation of Tregs from naïve T cells, TGF-β also promotes the generation of myofibroblasts from endothelial cells. The elevated production of myofibroblasts leads to enhanced recruitment

of inflammation cells and damage to aortic walls, followed by aggravation of aneurysms. Therefore, TGF-β may contribute to the pathogenesis of KD, but cease the inflammation by eliciting Tregs [62].

IL-35, an emerging cytokines, is produced mainly by nTregs in $CD4^+$ T cells [61]. Although the role of this cytokine in aneurysms is not clear, a recent report [63] showing that IL-35 infiltration in human atheroma plaques may merit further investigation into its contribution to aneurysms.

## 7 $CD8^+$ T cells

Accumulation of reports document that $CD8^+$ T cells infiltrate aneurysm lesion both from human and mice tissues [13,14,17,26,31,46,54,64–71]. The predominant cell types within the infiltrate in AAA tissues are $CD3^+$ T cells (more than 50%), including $CD4^+$ T cells and $CD8^+$ T cells [17]. $CD8^+$ T cells have been found, dating as far back as 1999, in AAAs rather than normal aorta. These $CD8^+$ T cells expressed well-characterized cytotoxic mediators, perforin and Fas, the death-promoting proteins. Perforin contributes to membrane damage and Fas acts by ligand-receptor interaction, which leads to the death of SMCs and elimination of elastin and collagen [70]. Consistent with this report, Dufner et al. [69] suggested that both peripheral and tissue percentages of $CD8^+$ T cells were enriched in AAA patients compared with healthy controls with increased production of IFN-γ and perforin. Similarly, further research showed that IFN-γ-producing $CD8^+$ T cells, but not $CD4^+$ T cells, contributed to aneurysm formation as shown by enhanced SMCs death and MMP-producing macrophage recruitment [68].

Brown et al. [64] suggested that $CD8^+$ T cells predominated over $CD4^+$ T cells in coronary artery aneurysms of acute Kawasaki disease (KD). This finding indicated that $CD8^+$ T cells' cytotoxic activity may be harmful to the pathogenesis of coronary aneurysm, with the potential mechanism of prolonging inflammation in arterial wall thereby promoting aneurysm formation [66].

It should be noted that there are subsets of $CD8^+$ T cells, and the roles of specific subpopulations in human and mice AAA, however, remains to be identified. Since circulating $CD4^+/CD31^+$ T cells have been reported to favor $CD8^+$ T cells proliferation and cytokine production in the aneurysmal arterial wall [54], the relationship between $CD4^+$ T cells and $CD8^+$ T cells in aneurysms needs to be confirmed.

## 8 γδ $TCR^+$ T cells

Besides αβ T cells infiltration in aneurysms, γδ T cells are also present and play an important role in aneurysms [19]. Most of the infiltrating T cells in Takayasu's arteritis (TA), a chronic inflammation response with hallmark of stenosis or aneurysm of large elastic arteries, consist of gamma delta (γδ) T cells. These cells in TA produced large amounts of IFN-γ rather than IL-4 and IL-10 [72]. But the lack of evidence about γδ T cells interaction with SMCs and other immune cells in classical aneurysms, such as AAA, propels us to identify their roles in atherosclerosis and other types of aneurysm.

## 9 Conclusion

T cells critically regulate aortic aneurysms by augmenting the chronic inflammation. While some T cell subsets aggravate aneurysms, other subsets or in some contexts they can limit inflammation and counteract protease activity. Experimental animal models have great help in confirming the role of these T cells in aneurysms, although many of them do not fully simulate human disease. Models that are close to human state should be developed to clarify which subsets are detrimental and which are potentially beneficial. Although our understanding of aortic aneurysms and their treatment has progressed, much remains unknown. Therefore, further mechanisms of T-cell-mediated regulation and cross-talk between activated T cell subsets and other immune cells are needed for effective treatment to prevent aneurysms expansion and rupture.

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